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Leukocytosis associated with clozapine in elderly patient

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ABSTRACT Clozapine is the second-generation antipsychotic which is approved by the US Food and Drug Administration for the treatment of refractory schizophrenia. Clozapine is unfortunately associated with number of adverse effects, one of the chief concerns is agranulocytosis and occasionally leukocytosis, i.e. elevation of white blood cell count. In some cases, the leukocytosis may be persistent. We report the case of a 65-year-old patient diagnosed with schizophrenia, who also fulfilled the criteria of treatment-resistant schizophrenia, treated with clozapine as patient experienced leukocytosis.

Key words: Clozapine, leukocytosis, refractory schizophrenia

INTRODUCTION

Clozapine is atypical antipsychotic used for refractory schizophrenia because of its therapeutic efficacy.^[1] Clozapine is a known risk factor for hematological side effects, such as agranulocytosis and neutropenia; however, blood dyscrasia such as leukocytosis is observed occasionally, which necessitate white blood cell (WBC) monitoring. The incidences of clozapine-induced hematological adverse effect in clinical trials are neutropenia 3%, agranulocytosis 1%, eosinophilia 1%, and leukocytosis are <1%.^[2]

Leukocytosis defined as a WBC count >11,000 cells/mm³. It has been associated with clozapine treatment, received less attention in literature. The clinical decision to continue or stop clozapine when leukocytosis develops could be a challenging task. Leukocytosis can occur as a result of physical and emotional stress, such as overexertion, seizure, anxiety, anesthesia, epinephrine administration,^[3,4] and infections. Other causes of leukocytosis that may be persistent include medications, splenectomy, hemolytic anemia, and

malignancy. Medications that have been reported to cause leukocytosis include corticosteroids, lithium and beta agonist.^[5] High smoking rates are also associated with increase total and differential WBC count.^[6]

Clinical manifestations of drug-induced leukocytosis include fever, malaise, and easy fatigue, but long-term side effects are unclear. As such, there are no guidelines to advise clinicians, if or when clozapine should be discontinued, if leukocytosis appears.^[1] There are no controlled data available to suggest antipsychotics treatment options if clozapine is discontinued because of associated hematological side effects.

CASE REPORT

A 65-year-old, well body built male belonging to low socioeconomic status, has been in psychiatric hospital, Taif in chronic rehabilitation ward since last 14 years. He was diagnosed with schizophrenia 35 years back. Despite being treated with multiple

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antipsychotics, he never achieved full remission, so we diagnose him as a treatment-resistant schizophrenia, and accordingly started treatment with clozapine. There is history of smoking since long and subsequently patient developed chronic obstructive pulmonary disease.

Clozapine was started 25 mg once daily, at that time his WBC count was 4490 mm³ and absolute neutrophil count (ANC) 3000 mm³. The clozapine dose was titrated according to the guidelines. At a dose of 100 mg daily of clozapine, WBC count increased to 7500 mm³ and ANC 5000 mm³. Moreover, it was observed that patient's WBC count was increased in parallel with increase of the clozapine dose. On the 10th week, clozapine dose was increased to 300 mg/day which showed significant rise in WBC count 19,000 mm³ and neutrophil count 15,400 mm³; however, complete blood count remains normal during treatment. Figure 1 depicts the total leukocyte counts findings and corresponding clozapine dose along with the number of days of clozapine use.

On physical examinations, vitals including temperature were within normal limit. The patient did not have any physical complaints or sign of infections but reported easy fatigability. The workup for infection, including chest X-ray, urine analysis, blood culture, stool analysis, hepatitis marker, and HIV testing were negative; other biochemical laboratory tests were normal. Two-dimensional echo was done to rule out myocarditis. Our medical specialist found no evidence of systemic illness and recommends hematological consultation.

It was decided to taper and discontinue clozapine despite improvement of psychotic symptom because repeated consultation and medical examinations found no evidence for the leukocytosis. He was put

on amisulpride 200 mg twice a day, after a week that improved his WBC count and ANC decreased and remains in the normal range. The patient was assessed on Naranjo scale, and the score was 6.

DISCUSSION

The mechanism of development of leukocytosis due to clozapine remains unknown.^[7] One possibility is that clozapine may stimulate the release of certain cytokines including tumor necrosis factor, interleukin (IL)-2, IL-6, and granulocyte colony-stimulating factor.^[8] Other possible risk factor may be smoking, being male in this case.

We reviewed the existing literature and many case reports on leukocytosis associated with clozapine is depicted in Table 1. Madhusoodanan *et al.*^[2] reported a case series of seven patients who developed chronic leukocytosis due to clozapine. None of the seven patients had any history of general medical conditions and infection. They opined that increased WBC count might be due to smoking and male gender as possible risk factors for leukocytosis. Polat *et al.*^[9] also reported case of 41-year-old women case of paranoid schizophrenia, treated with clozapine. She had no history of any medical condition except smoking as her one of the risk factors. Liu *et al.*^[10] also reported a case of 51-year-old man with long history of schizoaffective disorder, without any history of medical condition. However, clozapine was discontinued due to patient's refusal to do weekly WBC count test.

This case suggests that relationship between the use of clozapine and leukocytosis that is directly proportional. It was also observed that the rapid resolution of leukocytosis after the discontinuation of clozapine. Patient's WBC count and neutrophil count were within normal limit before initiating clozapine. The risk of the WBC count and neutrophil count was consistent with increase clozapine dose, suggesting a dose-dependent effect. When the clozapine dose was tapered down, the counts decreased proportionately. Moreover, the white cell count and neutrophil count come within normal range after the discontinuation of clozapine.

A medical workup to rule out the common cause of leukocytosis is the first step of management. It is also important to rule out possible risk factors to carry leukocytosis like medications such as lithium,

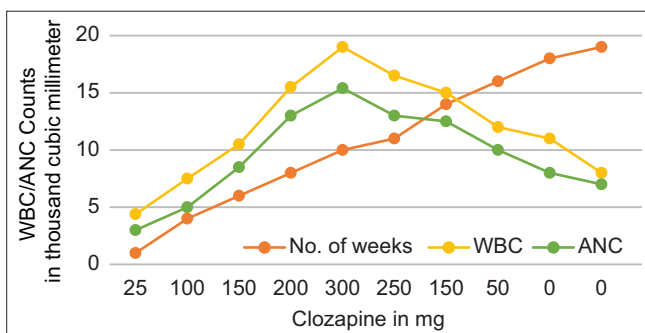


Figure 1: Patient's WBC and ANC in relation to clozapine dose and time. WBC: White blood cell, ANC: Absolute neutrophil count

Table 1: Nine case report review on leukocytosis with clozapine

Authors	Diagnosis	Clozapine dose (mg/day)	WBC count (mm ³)	Concurrent condition	Outcome
Polat et al. ^[9]	Paranoid schizophrenia	450	24,300	Smoking	Discontinued
Liu et al. ^[10]	Schizoaffective	400	22,300	Refusal to WBC test	Discontinued
Madhusoodanan et al. ^[2]	Paranoid schizophrenia	600	17,200	Smoking	Continued
	Schizoaffective	600	19,100	Smoking	Continued
	Paranoid schizophrenia	600	19,000	Smoking	Discontinued
	Paranoid schizophrenia	600	13,000	Smoking	Continued
	Paranoid schizophrenia	600	12,800	Smoking	Continued
	Undifferentiated schizophrenia	50	12,600	Smoking	Continued
	Paranoid schizophrenia	450	12,200	Smoking	Continued

WBC: White blood cell

prednisolone, beta agonist, epinephrine, anesthesia, smoking infections and inflammations such as tissue necrosis, burns, arthritis, and trauma. Medical conditions, such as infarction, seizure, splenectomy, hemolytic anemia and malignancy, should also be ruled out.

CONCLUSION

The incidence of leukocytosis associated with clozapine has been reported rarely in the literature. We observed dose-dependent effect, rise of WBC count and neutrophil count was consistent with increase of clozapine dose, the count decreased proportionately and became normal when there was discontinuation of clozapine.

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Conflicts of interest

There are no conflicts of interest.

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